

PROTOCOL

Study Title: Integrative Medicine for Hypermobility Spectrum Disorder (HSD) and Ehlers-Danlos (EDS) syndromes: A mixed-methods feasibility study

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PI: Douglas Hanes, PhD

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A. ABSTRACT

Hypermobility Spectrum Disorder (HSD) and Ehlers-Danlos syndromes (EDS) are debilitating conditions of the connective tissue that manifest in musculoskeletal complaints, joint dislocations or instability, skin and soft tissue anomalies, chronic pain, fatigue, GI disorders, headaches, blood pressure dysregulation, and have a negative impact on the psychosocial lives of many patients that suffer from the disorders. No unique genetic origin for HSD has been identified. However, among Ehlers-Danlos syndromes (EDS), the most common form of hypermobility, are 13 subtypes that are identifiable by their molecular defects.¹ Individuals afflicted with Hypermobility Spectrum Disorder (HSD) or Ehlers-Danlos syndromes (EDS) frequently remain undiagnosed for a significant length of time due to the variable symptoms of the disorder that overlap with other medical conditions. Treatments for HSD and EDS are inconsistent and lack a solid evidence base; in particular, the literature does not support the efficacy of physical rehabilitation.² While HSD and EDS are not curable, current strategies for managing the disorders commonly include a combination of physical, supportive, and behavioral therapies (such as education and coping strategies for managing the condition) in addition to pain killers.³ There are no large studies on holistic care among patients living with HSD or EDS, nor is there any research on dietary intake and its impact on the disorder.

The overall purpose of this study is to assess the feasibility of conducting a 9-week integrative medicine program that is comprised of a prescribed anti-inflammatory (Mediterranean) diet, as well as general behavioral and psychosocial support among patients with Hypermobility Spectrum Disorder (HSD) or

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Ehlers-Danlos syndromes (EDS), in order to determine the recruitment potential in this population and to measure the ability of individuals to complete the program. Participants will be prescribed a food plan, and adherence to and feasibility of the food plan will be measured through participant food tracking and a subjective assessment of the food plan in a brief satisfaction survey. This study aims to recruit 20 patients with HSD or EDS and make preliminary observations regarding the effects of integrative medical care on pain reduction and improved quality of life. Participants will be given a 1-week lead-in to track their general diet prior to starting their prescribed food plan, and associations will be recorded between symptom severity and diet as an exploratory analysis. Patient assessment of chronic illness care and living with a chronic illness will also be captured; to assess the experiences of patients with HSD or EDS, as well as their perceptions of previous medical care and patient-centered medicine, and any changes in these attitudes over the course of 9 weeks. Available studies assessing treatments for HSD or EDS provide insufficient evidence for treatment options; this project studies a novel intervention focused on nutrition and self-management counseling, developed in conjunction with a qualified physician, and would allow us to gain valuable information regarding the feasibility of employing the intervention as well as preliminary data on its effect on health outcomes.

B. SPECIFIC AIMS

B.1 Primary Aim: To investigate the feasibility of a 9-week integrative medicine intervention, as assessed by recruitment and retention in patients with Hypermobility Spectrum Disorder (HSD) or Ehlers-Danlos syndromes (EDS).

- Outcome Measures 1: The recruitment rate will be assessed as the number of participants enrolled per month, over the duration of open recruitment. Our goal is to recruit 20 participants within a span of 4 months. Retention rate will be determined as the proportion of participants completing the mid-study or end-of-study visits, with a goal of 75% retention for each study visit.

B.2 Secondary Aim: To evaluate the feasibility of and adherence to a prescribed food plan as well as the feasibility of food tracking as a part of a 9-week integrative medicine intervention in patients with Hypermobility Spectrum Disorder (HSD) or Ehlers-Danlos syndromes (EDS).

- Outcome Measures 2: To assess the feasibility of the dietary recommendations, adherence will be assessed using estimated daily dietary intake recorded in *MyFitnessPal*, a food tracker app for mobile devices and computers. The participant's reported macronutrient breakdown will be compared to the prescribed food plan to calculate an adherence score. Participants will also complete a food plan satisfaction survey at baseline, 5, and 9 weeks that will examine any physical side-effects, support needed, and any barriers to adherence, including food costs. The feasibility of food tracking will be measured by adherence to the recommended use of the app. A threshold of 3 days of reporting per week (including breakfast, lunch, dinner, and snacks) for the 9-week duration of the study will be considered adherent and should provide sufficient data to assess the observance of the recommended food tracking.

Protocol

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B.3 Tertiary Aim: To examine the effect of a 9-week integrative medicine intervention on overall perceived pain and quality of life in patients with Hypermobility Spectrum Disorder (HSD) or Ehlers-Danlos syndromes (EDS).

- Outcome Measures 3: Participants will complete a Visual Analog Scale for Pain (VAS Pain) and a 29-Item profile HRQoL Survey (PROMIS-29) at baseline, 5, and 9 weeks.

In order to better understand the needs of the patient population, we will also address the following exploratory aims, as far as we are able. These aims can be considered to be independent of the effects of treatment.

B.4 Exploratory Aim 1: To evaluate any associations between symptom severity, perceived pain, quality of life, and diet among patients with Hypermobility Spectrum Disorder (HSD) or Ehlers-Danlos syndromes (EDS).

- Participants will be given a 1-week lead-in to establish baseline food patterns before starting the prescribed food plan. Associations of dietary composition, patient-reported symptoms, as well as overall perceived pain and quality of life scores will be examined, both cross-sectionally at intake and longitudinally over the 9 weeks of the intervention.

B.5 Exploratory Aim 2: To assess the experiences of chronic illness care and living with chronic illness among patients with Hypermobility Spectrum Disorder (HSD) or Ehlers-Danlos syndromes (EDS).

- Outcome Measure 5: Participants will complete a 26-item survey, Patient Assessment of Chronic Illness Care (PACIC+), that evaluates areas of patient self-management within the chronic care model of healthcare. The PACIC+ ascertains attitudes regarding patient-centered care, living with chronic illness, and chronic illness care; it will be completed by participants at baseline and 9 weeks.

C. BACKGROUND AND SIGNIFICANCE

C.1. History and Prevalence

Ehlers–Danlos syndromes (EDS) are a categorically distinctive set of connective tissue disorders with a varied range of symptoms characterized by generalized joint hypermobility, loose ligaments, and joint pain.⁴ Initially, the prevalence of EDS was thought to be 1 in 5,000 individuals; however, these figures have been disputed more recently, and it is proposed that there is a lack of screening and early detection for the disorder due to the misconception that it is rare, which may contribute to underreporting.^{5,6} There are 13 subtypes of EDS recognized by the International EDS Consortium that are genetically heritable; however, Hypermobile Ehlers–Danlos syndromes (hEDS) are heterogeneous, meaning the exact gene responsible for the disorder is unknown.⁴ Next-generation sequencing (NGS) has identified faulty collagen production as a potential genetic cause, however, not all EDS subtypes possess this mutation.⁷

Protocol

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Hypermobility Spectrum Disorder (HSD) is the umbrella term for joint hypermobility in 4 or more joints in the body for which a genetic mutation for the disorder is unknown. A diagnosis of HSD usually occurs after Ehlers–Danlos syndromes (EDS), which can be tested both genetically and clinically, have been ruled out.

C.2 Signs and Symptoms

HSD and EDS are often undiagnosed, even with regular recurrence of symptoms and repeated medical appointments over an extended period of time. The diagnosis for the condition relies solely on clinical observations, and the disorders are frequently associated with a range of comorbidities that vary widely among afflicted patients and can easily present as the main concern. In a retrospective cohort study of patients with EDS, they were found to be 7.38 times more likely to suffer from abdominal pain, 4.07 times more likely to have neuropathic pain, 5.21 times more likely to have migraines, 2.85 times more likely to have joint pain, and 5.55 times more likely to have fatigue than those without the disorder.⁸

Observed rheumatologic presentations of HSD and EDS include fatigue, musculoskeletal pain, joint instability, or dislocation resulting in subluxations, and muscle weakness.⁹ Cutaneous or symptoms related to the skin include sprains, abnormal wound healing, mitral valve prolapse, propensity for temporomandibular joint disorders (i.e. TMJ), asthma as the result of lung atopy, constipation, gastroparesis, and other GI disorders related to motility.¹ Skin hyperextensibility may also result in menstrual and sexual problems in women, often in conjunction with pelvic prolapse.¹ Neurological disorders that accompany HSD and EDS include migraine headaches, loss of proprioception (sense of position), dysautonomia, or dizziness as the result of low blood pressure and an overly compensatory heart rate, depression, anxiety, and poor quality of life.¹ Immunological disorders associated with HSD and EDS include mast cell disorders as the result of histamine dysregulation and auto-immune disorders related to the connective tissue in the body.¹⁰

An often overlooked outcome of HSD and EDS, its psychosocial impacts were assessed through qualitative interviews, revealing common themes among patients with the disorder that included restricted daily activities due to fatigue or pain, feelings of burdening others, a lack of independence, healthcare limitations (including a lack of awareness of HSD or EDS from providers), social stigma, fear of the unknown, as well as reported difficulty with coping.¹¹ In a prospective cohort study of 158 subjects, it was found that HSD was associated with a higher risk of developing panic disorders.¹²

C3. Diagnosis

For most patients suffering from HSD and EDS, receiving a diagnosis is problematic as manifestations of the disorder are often vague, multifactorial, or ubiquitous. Because of common comorbidities, many of the clinical findings frequently will not align with standard HSD and EDS signs and symptoms; consequently, the condition is not always assessed or identified by healthcare providers.¹³ There is no definitive biomarker for HSD and EDS. A diagnosis, however, can be validating and essential to management, treatment, and recovery. Since many patients with HSD and EDS have complex medical

Protocol

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histories, in conjunction with comorbidities such as depression and anxiety, they often feel discredited and alienated when they do seek out healthcare.¹¹ It also remains unknown whether the chronic pain associated with HSD and EDS is the result of psychosocial impairment or whether it is a direct consequence of the disorder itself.¹³

To diagnose joint hypermobility, a series of 9 maneuvers assess standard range of motion measurements; or angles on what is called a Beighton scale. For every motion for which hyperextension of the joint is present, a score of 1 point is documented.¹⁴ A score of 4/9 or more indicates the presence of generalized joint hypermobility. The term “joint hypermobility” represents laxity in the joint, and it is important to emphasize that HSD and EDS are not diseases, but are instead, the presentation of a connective tissue disorder.¹

A Beighton score may be negative after the age of 33, even in individuals with a previous EDS or HSD diagnosis, as joint laxity decreases with age, even when pain and other manifestations of the disorder remain from previous hypermobility.³ In a systematic review of the Beighton score, it was found to be a reliable but not a valid instrument; meaning it has demonstrated uniform measurement (carried out clinically), however, as a diagnostic tool for measuring hypermobility, it may not be conclusive.¹⁵

C4. Treatment

The most prominent symptom associated with HSD and EDS is pain that is often life-altering and disabling. Since subluxations are often involuntary and happen spontaneously, some patients may only have mild pain associated with these occurrences. Chronic pain unrelated to these frequent dislocations is strongly associated with HSD and EDS, however, and it is both physically and psychologically disabling.¹⁶ In a study among Dutch patients with EDS, 90% were reported to suffer from pain, with Hypermobile Ehlers–Danlos syndromes (hEDS) patients having the most elevated pain severity scores among the cohort.¹⁷ In a study of pressure pain thresholds, it was found that 50% of patients with Ehlers-Danlos syndrome hypermobility type (hEDS) experienced neuropathic pain when compared to healthy individuals.¹⁸ Another reported feature of HSD and EDS is hyperalgesia, or pain hypersensitivity, which may be an additional indication of central nervous system damage as a result of the disorder.¹⁸ Taking into consideration that chronic pain can be neuropathic; or related to a potentially damaged nervous system or nociceptive, where the pain is linked to inflammation from a tissue injury, pain medications may be entirely ineffective.³

Overall, pharmaceutical interventions and standard of care for HSD and EDS vary, and currently, there are no drugs that specifically target connective tissue defects. Along with pain management, patient-centered medical care that supports effective coping strategies, as well as social support, might contribute to better management of the disorders. Previous studies have concluded that the social environment is essential for pain management, and by facilitating acceptance of their diagnosis, patients may gain the necessary coping techniques to establish a new ‘normal’ life.¹⁹ A mixed-methods study of 38 patients with HSD and EDS receiving physical therapy found that patients had lower health-related quality of life (HRQoL) scores than the average American adult and a perceived a need for a “whole-

Protocol

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body approach, long-term maintenance care, incorporation of multiple rehabilitation techniques, and patient-centered care that addresses safety and stability.”²⁰ A shift to a patient-centered model of chronic illness care could provide patients with a more active role in their own treatment, validate their experiences, and provide emotional support for coping.

C5. Anti-inflammatory (Mediterranean) diet

Hypermobile Ehlers–Danlos syndromes (hEDS) are shown to be associated with rheumatological diagnoses, some of which are inflammatory, and cells with hEDS and HSD specificity appear to have inflammatory cytokines *in vitro* even though they are genetically distinct disorders.^{21, 22} Inflammatory cytokines are often targeted with an anti-inflammatory diet that avoids foods like wheat, sugar, refined oils, trans fats, fast food, or any other processed foods and meats. Anti-inflammatory diets encourage increasing whole fruits, vegetables, and grains as well as balancing macronutrients (proteins, carbohydrates, and fat) for every meal. The most researched anti-inflammatory diet, the Mediterranean diet, was shown in a systematic review of 46 observational studies to be associated with a reduction of inflammatory biomarkers.²³ An anti-inflammatory food plan may provide some support for chronic pain that is associated with HSD and EDS.

C6. Integrative Medicine Approach

The complex nature of both HSD and EDS and the various comorbidities that arise may necessitate an intervention that incorporates more than pain management. Psychosocial support that is incorporated into coping approaches that were found in qualitative interviews among patients with HSD and EDS to provide support were acceptance, building social awareness, and education about joint hypermobility as well as physical modifications that could be made.¹¹ Patient-based care may mitigate some of the complications that accompany chronic illnesses, and by facilitating effective coping strategies that incorporate social support, a patient can feel supported by a comprehensive care management team.¹¹ In a narrative review of Ehlers–Danlos syndrome (EDS), the four common psychosocial conditions that were found to be consistent in the literature were “cognitive problems (and attention to body sensations), negative emotions, and unhealthy patterns of activity (hypoactivity/hyperactivity).”²⁴ The authors concluded that because chronic pain can be so invalidating, incorporating psychosocial support is essential to rehabilitation, especially when the patient is not responsive to conventional treatment.²⁴

Integrative medicine may provide some support for chronic illnesses, as it relies upon a patient-centered model of healthcare, one defined by the Academy of Integrative Health and Medicine (AHIM) as “an approach that rather than a disease-focused model, is instead a wellness and prevention model. Integrative health must also include not only our individual selves, but our community, our environment and our planet.”²⁵ As can be seen in Figure 1., in the Integrative Care Model, the patient is in control over their own illness, and the therapeutic relationship they establish with their healthcare providers promotes autonomy, decision-making, and being treated as a whole person.

Protocol

Study Title: Integrative Medicine for Hypermobility Spectrum Disorder (HSD) and Ehlers-Danlos (EDS) syndromes: A mixed-methods feasibility study (IMforHSDandEDS)

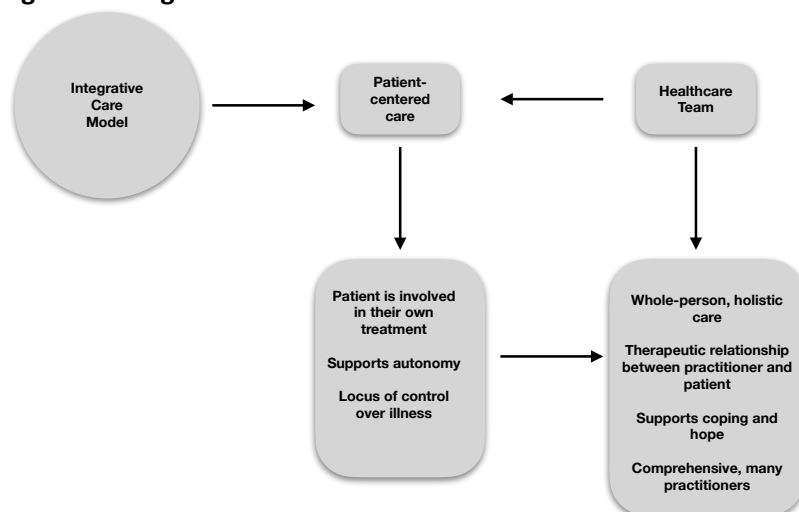
PI: Douglas Hanes, PhD

IRB #: DH10320/PRAF

Approval Date: 01.05.21

Version: 2.0

Figure 1. Integrative Care Model



D. Preliminary Data

D.1 Preliminary Data

No preliminary data exists at this time.

E. RESEARCH DESIGN AND METHODS

E.1. Overview

This feasibility study will investigate the recruitment potential and retention rate among patients with Hypermobility Spectrum Disorder (HSD) or Ehlers-Danlos syndromes (EDS) participating in a 9-week integrative medicine intervention that involves a prescribed anti-inflammatory (Mediterranean) diet, as well as general behavioral and psychosocial support. The feasibility of the food plan will also be examined through participant food tracking as well as through a food plan assessment in a brief satisfaction survey. Up to 20 patients with HSD or EDS will be enrolled from the Portland Oregon area, and the in-person screening study visit and the 2 virtual follow-up visits will be conducted at or from the Healthy Living Community clinic. We will also obtain preliminary data on any effects that the 9-week integrative medicine intervention has on pain and health-related quality of life. Outcome measures will be collected at 5 and 9 weeks, with the exception of the patient assessment of care for chronic conditions (PACIC+), that will be collected at baseline and the close-out visit during week 9.

Figure 2. Study Design

Protocol

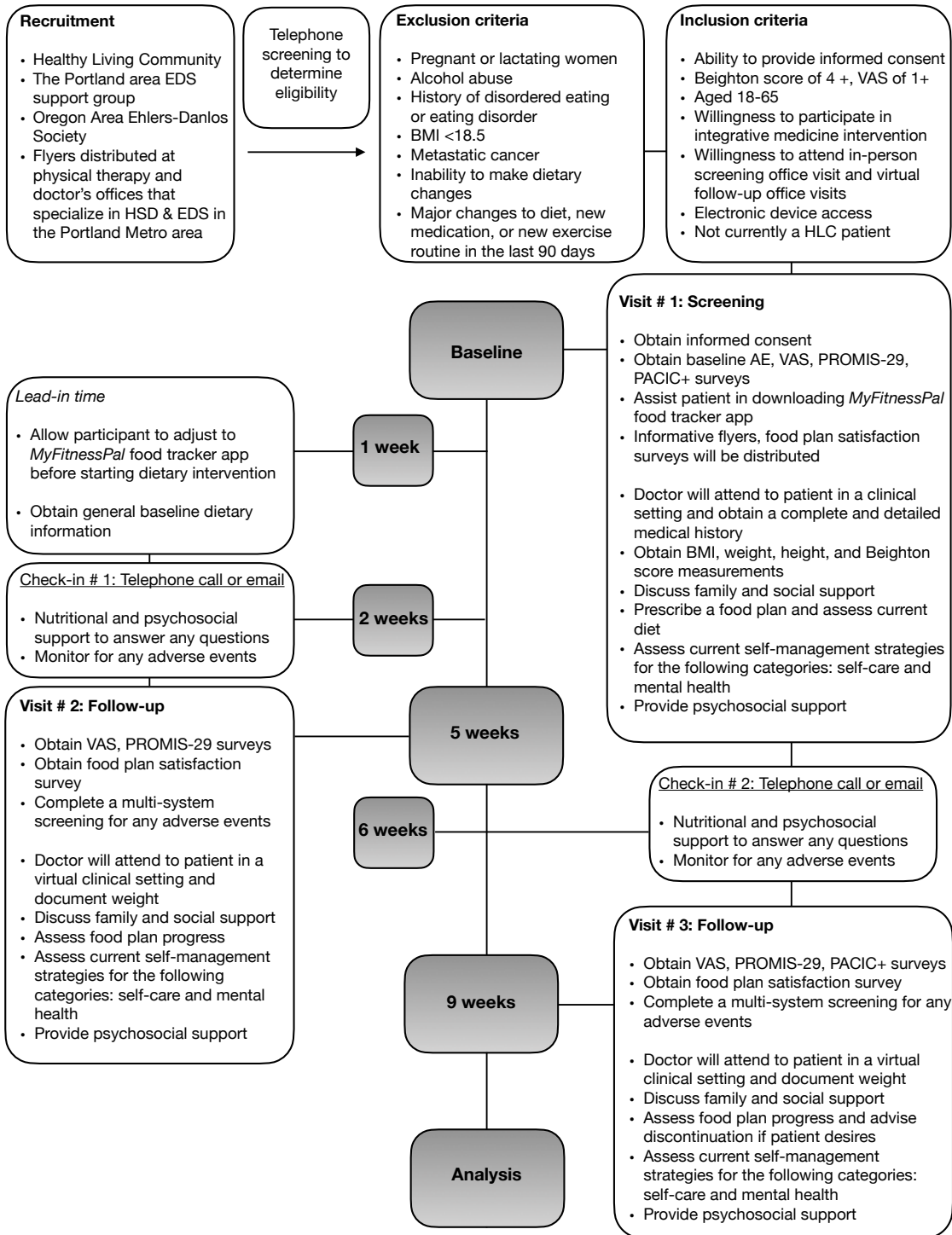
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E.2 Recruitment

Participants will be recruited from a local nonprofit private medical practice in Portland, Oregon, Healthy Living Community. We will post advertisements via the Healthy Living Community email newsletter, Facebook page, as well as in the doctor's office. (See Appendices 6A and 6B)

We will also post flyers through the Portland area EDS support group, Oregon Area Ehlers-Danlos Society, as well as local physical therapy and doctor's offices that specialize in HSD and EDS in the Portland Metro area. The flyers will invite patients who believe that they have HSD or EDS and are in pain to participate in the study.

Healthy Living Community and Dr. Schaefer have a social media presence that may build trust among a more racially and ethnically diverse study population and help participants to research the practice and feel comfortable ahead of time. While it would greatly enhance generalizability of results, if we were able to stratify recruitment to specifically include minorities and diversify study participants, we do not consider this feasible in the current pilot study of a small local population, in which the primary barrier is to a sufficiently large sample of any demographic composition.

E.3 Participant Population

All participants will be required not to be current patients for Dr. Schaefer and Healthy Living Community. The Clinical Investigator, Dr. Schaefer, will confirm the HSD or EDS diagnosis during the in-person screening visit, where range of motion measurements will be obtained. Up to 20 participants will be enrolled with a Beighton score of 4 or above, which indicates the presence of generalized joint hypermobility.¹⁴ A baseline Visual Analog Scale for Pain (VAS Pain) indicating pain at a level of 1 or above will also be required for enrollment.

E.3.1 Inclusion Criteria

- Age 18-65
- Beighton score of 4 or more to confirm joint hypermobility diagnosis
- Baseline VAS Score of 1 or more
- Not currently, or already a patient of Dr. Schaefer and Healthy Living Community
- Ability to provide written informed consent
- Willingness to participate in 9-week integrative medicine intervention (and make dietary and lifestyle changes)
- Willingness to attend 1 in-person screening visit and 2 virtual office visits
- Access to an electronic device for *MyFitnessPal* food-tracker use (i.e mobile device, tablet, laptop)

E.3.2 Exclusion Criteria

- Pregnant and lactating women, or planned pregnancy over the next 3 months

Protocol

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PI: Douglas Hanes, PhD

IRB #: DH10320/PRAF

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Version: 2.0

- Consumption of more than 14 (men) or 7 (women) alcoholic drinks per week
- History of disordered eating or eating disorder
- Body mass index (BMI) considered underweight (<18.5)
- Weight loss from metastatic cancer
- Unable to make dietary changes or participate in a 9-integrative medicine nutritional intervention
- Those with significant dietary changes, new medications, or new exercise routines within the past 90 days
- Currently, or already, a patient of Dr. Schaefer and Healthy Living Community

E.4 Participant and Procedure Schedule

E.4.1 Overview

The study is comprised of 1 in-person screening, 2 follow-up visits, and 2 telephone or email check-in correspondences for additional support. The in-person screening and 2 virtual follow-up visits will take place at the Healthy Living Community clinic. Virtual follow-up study visits will take place via the Zoom video platform utilized by ChARM TeleHealth, a web-based and HIPAA compliant server maintained by the Healthy Living Community clinic and will occur at 5- and 9-weeks post-enrollment.

During the in-office screening, participants will have their joint mobility measured in accordance with the Beighton Scoring System to confirm that they meet the diagnostic criteria for Hypermobility Spectrum Disorder. Participants who are diagnosed using the Beighton criteria and meet other eligibility criteria will then be asked to provide informed consent (E.4.3) and enrolled in the study if willing. The Clinical Investigator will capture a complete and detailed medical history of enrolled participants, discuss family and social support, as well as prescribe a food plan. The CI will also assess the patient's current self-management strategies and provide general behavioral and psychosocial support. During the 2 follow-up visits, the Clinical Investigator will revisit these self-management strategies. As scheduling visits may be difficult at precisely 5 and 9 weeks, we will leave some flexibility for these points in time to accommodate the schedules of the Clinical investigator, the student researcher, and the participants.

At 2 and 6 weeks, the participants will be contacted by the student researcher to answer any questions, provide nutritional and psychosocial support, monitor for any adverse events, and offer solutions to any dietary challenges. Participants will also be assessed at all study visits for any adverse events.

Participants will be asked to complete pain (VAS), and health-related quality of life (PROMIS-29) instruments at baseline, 5, and 9 weeks. Adherence to the dietary recommendations, as well as the feasibility of food tracking will be obtained using *MyFitnessPal*, a food tracker app throughout the 9 weeks. A food plan satisfaction survey will be collected at 5 and 9 weeks. Participants will fill out the patient assessment of care for chronic conditions (PACIC+) at baseline and the close-out visit during week 9.

Protocol

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E.4.2 Telephone Screening

Prospective participants will be contacted via telephone prior to their first visit. A standardized telephone script will be used to determine, as far as possible, if the participants meet the inclusion criteria and are eligible to join the study (See Appendix 3A).

In event that a prospective participant does not know if they have a Beighton score of 4 or more, a free screening will be required before scheduling the Screening visit. The medical assistant at Healthy Living Community clinic will confirm that prospective participants meet the eligibility requirements but will not record or capture any data. This will prevent prospective participants that are ineligible for the study from being scheduled for a screening visit. After the Beighton score is visually confirmed, the prospective participant will have the option to re-screen by telephone for the study and then be scheduled for a Screening Visit with the Clinical Investigator, if eligible.

E.4.3 Informed Consent

Informed consent paperwork will be sent to the participant before their first visit so that they can review the document, but they will not sign anything until the first study visit. The study participants will meet with the student researcher to answer questions and to look over the consent forms prior to signing the document. The signed informed consent paperwork will be captured electronically via REDCap, a secure and HIPAA compliant web-based application used to capture electronic data for research studies (See Appendix 2B).

E.4.4 Visit # 1: Screening (baseline)

During the in-person screening visit, CDC Coronavirus Disease 2019 (COVID-19) doctor visit regulations will be followed, and all participants, the student researcher, and the Clinical Investigator will be required to wear facial masks, maintain a physical distance at 6 feet apart, and wash hands after all contact.²⁶

Participants will review the informed consent form with the student researcher, who will answer any questions. A signed form will be collected prior to initiating study-related activities. The Clinical Investigator (CI) will take range of motion measurements that will be obtained in accordance with The Beighton Scoring System to confirm that the participant meets the diagnostic criteria for Hypermobility Spectrum Disorder. BMI, height, and weight will also be collected. Participants will be screened for a history of disordered eating or eating disorders; if present; the participant will be referred to a specialized physician for treatment and excluded from the study. Participants with a body mass index (BMI) considered to be underweight, or less than 18.5, will also be excluded from the study.²⁷ The CI will calculate the daily caloric needs for each patient using the estimated energy requirements (EER) formula for each patient that takes into consideration their current physical activity level (i.e. sedentary or active), weight, and age.²⁸ The CI will request consent to obtain the medical records of the participant.

The Clinical Investigator will do a thorough review of the patient's full medical history and listen to their entire background. They will discuss the social and familial support of the patient, assess their general diet, provide psychosocial support, and prescribe an anti-inflammatory food plan. The Clinical

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Investigator will also assess the patient's current self-management strategies and provide general behavioral and psychosocial support. Any current medications or supplements being used for pain that the participant is taking will also be documented, but no changes in medications will be required by the study. Participants will be given portal access to their electronic health records through ChARM Patient Portal for the use only of this study.

The student researcher will assist participants with logging into REDCap and collecting baseline pain (VAS), health-related quality of life (PROMIS-29) and patient assessment of care for chronic conditions (PACIC+) surveys. A baseline adverse events questionnaire will be obtained using the NUNM standardized multi-system survey for each participant, to document any current health conditions that may not be listed in the medical record. Participant demographic information will be collected, including age, sex, and gender

The student researcher will provide flyers with advice and guidelines for following a meal plan that follows an anti-inflammatory eating pattern, including recommendations for meal planning and strategies for adding and reducing certain foods (See Appendices Gi through Giv). The macronutrient breakdown that will be recommended for the patients will be 40- 50 % carbohydrate, 15- 20 % protein, and 35- 40 % fat,²⁹ which is aligned with the Mediterranean-style eating pattern and has been shown to be anti-inflammatory.²³ Participants will be provided a food plan that is in accordance with their current average dietary consumption of either 1800 or 2200 calories. (See Appendices 2Gi through 2Giv) Participants will also be given a list of resources for online and local Mediterranean-style eating patterns to simplify their research options. (See Appendix 2Gvi)

The student researcher will assist participants with downloading *MyFitnessPal* so that their estimated daily dietary intake can be captured. Participants will be assigned a *MyFitnessPal* username using an unidentifiable study number that will be recorded by the student researcher in a secure location, and the account will only be used for study purposes. Participants will be instructed that no identifiable health data related to the study will be shared on the *MyFitnessPal* app. The student researcher will also review the Sharing & Privacy settings in the *MyFitnessPal* app with participants to ensure that the privacy is protected as much as possible.

They will also provide a handout for how to use the app or website (See Appendix 2Gv). Participants will be given an opportunity to practice using the app with support from the study coordinator. Participants will be encouraged to track their diet daily to the best of their ability and will be able to opt-out of tracking if they express concerns. Using the Friends feature on the app, participants will be able to share their daily food tracking with the student researcher, and the data will be collected at 5 and 9 weeks. Participants will be given a 1-week lead-in period so that they can adjust to tracking their dietary intake before starting the food plan and will be instructed to contact the student researcher with any questions.

E.4.4.1 Food Plan Satisfaction Survey

Protocol

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IRB #: DH10320/PRAF

Approval Date: 01.05.21

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We will distribute food plan satisfaction surveys via REDCap to be completed by the participant prior to the patient's next visit (5 weeks). The surveys will gather information regarding the overall cost-effectiveness and feasibility of the diet and any obstacles that are faced with the food plan. (See Appendix 2Fi)

E.4.5 Check-in #1 (2 weeks)

Participants will receive a phone call or e-mail from the student researcher that will answer any questions, provide nutritional and psychosocial support, and offer solutions to any dietary challenges. The goal is to provide support with dietary adherence. This will occur 4 weeks after Visit # 1 and will be set up in advance at a time that works for the participant. If the participant is not available, we will send a check-in email and answer any questions, provide nutritional and psychosocial support, and offer solutions to any dietary challenges by email, if requested. The nutrition counseling script contains suggestions for a general healthy eating pattern but is not a part of food plan adherence. (See Appendix 3B)

Participants will be assessed for any adverse events with the following question, "Are you experiencing any new symptoms or side-effects that you may have noticed?" (See Appendix 3B)

E.4.6 Visit # 2: Follow-up (5 weeks)

During the second virtual clinical visit, the student researcher will collect VAS pain measurements, health-related quality of life scores (PROMIS-29) and will assess for any adverse events using the NUNM standardized multi-system questionnaire.

The Clinical Investigator will discuss the social and familial support of the patient, provide psychosocial support, and address any concerns with the anti-inflammatory food plan. The CI will also assess the patient's current self-management strategies and provide suggestions for any adjustments to general behavioral and psychosocial support recommendations. Any current medications or supplements being used for pain that the participant is taking will also be documented, but no changes in medications will be required by the study. Current self-reported weight will also be documented.

E.4.6.1 Food Plan Satisfaction Survey

We will distribute food plan satisfaction surveys via REDCap to be completed by the participant prior to Visit # 3. (See Appendix 2Fii)

E.4.7 Check-in #2 (6 weeks)

Participants will receive a phone call or e-mail from the student researcher that will answer any questions, provide nutritional and psychosocial support, and offer solutions to any dietary challenges. The goal is to provide support with dietary adherence. This will occur 1 week after Visit # 2 and will be set up in advance at a time that works for the participant. If the participant is not available, we will send a check-in email and answer any questions, provide nutritional and psychosocial support, and offer solutions to any dietary challenges by email, if requested. The Nutrition counseling script contains

Protocol

Study Title: Integrative Medicine for Hypermobility Spectrum Disorder (HSD) and Ehlers-Danlos (EDS) syndromes: A mixed-methods feasibility study (IMforHSDandEDS)

PI: Douglas Hanes, PhD

IRB #: DH10320/PRAF

Approval Date: 01.05.21

Version: 2.0

suggestions for a general healthy eating pattern but is not a part of food plan adherence. (See Appendix 3B)

Participants will be assessed for any adverse events with the following question, “Are you experiencing any new symptoms or side-effects that you may have noticed?” (See Appendix 3B)

E.4.8 Visit # 3: Follow-up (9 weeks)

During the final virtual visit, the student researcher will collect VAS pain measurements, patient assessment of care for chronic conditions (PACIC+), PROMIS-29 health-related quality of life scores and will assess participants for any adverse events using the NUNM standardized multi-system questionnaire.

The Clinical Investigator will discuss the social and familial support of the patient, provide psychosocial support, and address any concerns with the anti-inflammatory food plan. The CI will also assess the patient’s current self-management strategies and provide suggestions for any adjustments to general behavioral and psychosocial support recommendations. Any current medications or supplements being used for pain that the participant is taking will also be documented, but no changes in medications will be required by the study. Current self-reported weight will also be documented.

At the final visit, patients will be encouraged to continue to eat a healthy diet but will be reminded that the study is complete and that they may alter their diet in whatever way they wish.

E.5 Intervention

9-week integrative medicine intervention

Enrolled participants will take part in a 9-week program that includes a novel integrative medicine intervention that is focused on patient-centered care. The patient will establish a therapeutic relationship with a holistic healthcare provider team consisting of a medical doctor and a student researcher to support comprehensive care. Participants will attend a total of 3 visits with a medical doctor over the 9-week integrative medicine intervention.

The Clinical Investigator has created a 9-week program that is composed of a prescribed anti-inflammatory (Mediterranean) food plan as well as general behavioral and psychosocial support. During the 3 consultations with the participant, the CI will: 1) Capture a complete and detailed medical history and background, 2) Discuss familial and social support, 3) Provide psychosocial support, 4) Assess the patient’s current self-management strategies for self-care, and 5) Assess the patient’s current self-management strategies for mental health. Study personnel will also follow provide psychosocial and nutritional support to address any additional concerns and promote adherence to the food plan.

Prescribing an anti-inflammatory food plan and assessment of current diet

Protocol

Study Title: Integrative Medicine for Hypermobility Spectrum Disorder (HSD) and Ehlers-Danlos (EDS) syndromes: A mixed-methods feasibility study (IMforHSDandEDS)

PI: Douglas Hanes, PhD

IRB #: DH10320/PRAF

Approval Date: 01.05.21

Version: 2.0

The Clinical Investigator will prescribe an anti-inflammatory food plan that consists of a high intake of fruits and vegetables (4-5 serving of each per day).³⁰ The specific dietary requirements for adherence to the anti-inflammatory food plan incorporated in this 9-week integrative medicine intervention will include macronutrient levels similar to those of a Mediterranean diet, which breaks down to 40-50% carbohydrates, 15-20% protein, and 35-40 % fat.²⁹ Such a diet is high in fiber, micronutrients, healthy fats, and antioxidants that may provide health benefits by reducing inflammation.²³ The Clinical Investigator will present the macronutrient requirements, assess the current diet of the participant, and suggest modifications that will cause their diet to conform to study guidelines, such as reducing sugar as well as processed and fast foods. They will discuss removing trans fats and hydrogenated oils and replacing them with cold-pressed and unrefined oils. For simplicity and accuracy, participants will be advised to follow a “Mediterranean-style eating pattern,” which is very searchable among recipe databases and websites, and more specific than the term “anti-inflammatory.”

Participants will be provided an anti-inflammatory food plan that includes recipes, a guide for adding and reducing certain foods, and obtaining targeted macronutrient levels (see above) if modification of their current diet seems infeasible, or if they so desire. The student researcher will assess the cooking skills of participants and provide resources, as needed (i.e. YouTube channels, websites). They will discuss meal-planning, meal-prepping, and making a grocery list on a budget as needed. Additionally, participants will be contacted twice via phone or email by the student researcher to provide nutritional and psychosocial support, answer any questions, and facilitate adherence.

Capturing a complete and detailed medical history and background

The Clinical Investigator will comprehensively intake the patient’s full medical history and listen to their entire background. Because HSD and ESD can be a frustrating and invalidating prognosis, extreme sensitivity and empathy will be used to build trust and develop a therapeutic relationship with the participants.

Patients suffering from these conditions report that the limitations they receive within the healthcare system often involve a lack of awareness of HSD or EDS from providers, and hold similar perceptions that they have been ignored, belittled, or considered to have hypochondria when they do seek advice.¹¹ The Clinical Investigator will approach the participants by validating their experience with an emphasis on reinforcing the feeling that participants are and being heard, believed, and listened to attentively.

Discussing familial and social support

The Clinical Investigator will assess what and intrapersonal support the participants have, which can help influence long-term health changes. Motivational interviewing will be utilized and “include *engaging* with patients to help build rapport, *focusing* patients on the changes they want to make while offering advice and support, *evoking* the tools, and desires they possess within them to effect change, and *planning* to implement the goals and next steps patients identified through the encounter.”³¹

Protocol

Study Title: Integrative Medicine for Hypermobility Spectrum Disorder (HSD) and Ehlers-Danlos (EDS) syndromes: A mixed-methods feasibility study (IMforHSDandEDS)

PI: Douglas Hanes, PhD

IRB #: DH10320/PRAF

Approval Date: 01.05.21

Version: 2.0

The Clinical Investigator will assess the general support that the participants have in their home, or in the community where they live, to make dietary and lifestyle changes. This will involve discussing any barriers they have, such as grocery store and transportation access, and practical needs like having a kitchen, tools to cook, or time to prepare fresh food. Potential solutions to these barriers like community food pantries and cooking classes will be recommended depending on the location of the participant. The CI will also assess the social network of the participant for supportive relationships that are necessary to create healthy behavior changes. Recommendations will be made in accordance with the needs of the participant and may include referrals to the Portland area EDS support group, or Oregon Area Ehlers-Danlos Society if they require more assistance.

Providing psychosocial support

Psychosocial support will be provided by both the Clinical Investigator, the student researcher, and *MyFitnessPal* throughout the 9-week program. Participants will receive behavioral, lifestyle, and dietary counseling all through a total of 3 office visits with the medical doctor, and 2 phone calls or e-mail check-in correspondences with the student researcher.

The student researcher has personal experience with both hEDS and Postural Tachycardia Syndrome (POTS), and similar to another EDS study, this will be disclosed to participants at the beginning of the interview in an effort to mitigate the power imbalance that often accompanies research.¹¹ This may also help “instill greater confidence in participants” to share their experiences with a researcher and EDS individual who is also in their “in-group.”¹¹ It will also be “emphasized that it [is] their stories that matter” for the purpose of the study.¹¹

MyFitnessPal

MyFitnessPal, a food tracker available on both Apple and Android for mobile devices, as well as both Windows and Mac computer platforms, will be used to collect estimated daily dietary intake for participants. *MyFitnessPal* has a database of nutritional information for over 11 million foods that will allow participants to capture their general diet by manually adding individual ingredients, barcode scanning, or finding whole meals.³² In a comparison of micronutrients and calories between diet-tracking apps and the USDA database, *MyFitnessPal* was shown to have the best coding accuracy.³³ Self-reported data, however, may be subject to inaccuracies. When foods are entered into the *Diary* feature located in the app, the *Nutrient Dashboard* displays daily calories, as well as macronutrient proportions, broken down into carbohydrates, fats, and protein.

Participants will be encouraged to track their daily diet to the best of their ability, and for weeks that there is missing data, a threshold of no less than 3 days of tracking (including breakfast, lunch, dinner, and snacks) per week for the 9-week study duration will be considered adherent and averaged appropriately. Individuals with previous disordered eating patterns, or discomfort with food tracking, will be able to opt-out; however, they will still be shown how to use *MyFitnessPal* to analyze dietary

Protocol

Study Title: Integrative Medicine for Hypermobility Spectrum Disorder (HSD) and Ehlers-Danlos (EDS) syndromes: A mixed-methods feasibility study (IMforHSDandEDS)

PI: Douglas Hanes, PhD

IRB #: DH10320/PRAF

Approval Date: 01.05.21

Version: 2.0

composition for adherence. A 1-week lead-in prior to introducing the food plan will be utilized to provide a baseline record of the participant's general diet. *MyFitnessPal* data will allow us to track general adherence to dietary changes, the overall quality of the participant's diet, and average macronutrient proportions. By measuring the participant's reported macronutrient percentage scores and comparing them with the prescribed food plan, we will be able to calculate an adherence score.

MyFitnessPal usage has been shown to have positive results for behavioral and health changes, and for meeting nutrition-related goals, and was found to be associated with higher levels of reported self-efficacy among users that reported more frequent use.³⁴ In a systematic review of dietary mobile app use and chronic diseases, it was concluded they may be effective self-monitoring tools and were shown to have positive effects on measured nutritional outcomes.³⁵ Other small studies have shown that wearable technology may provide additional psychosocial support for dietary interventions and behavioral change.³⁶ Most health and fitness apps have also been shown to incorporate health behavior theory, which is essential for behavioral change.³⁷ In a focused review of smartphone diet-tracking apps, *MyFitnessPal* was shown to have better usability when compared to other apps; however, one disadvantage that the review cited for all diet-tracking apps was that users lack the ability to track their emotions.³³

Assessing the patient's current self-management strategies for self-care

The Clinical Investigator will assess each participant's self-care regime and make recommendations. They will make the following mindfulness, sleep, and movement recommendations listed below.

Practice mindfulness: Have some quiet time to yourself once a day. Listen to a guided meditation or grab a journal. Write down your thoughts. Let go of stress and try to relax. Try chanting, prayer, or using a mantra.

Mindful eating: Take some time to slow down and eat your food. This will help you tune in with your body. It might take time to listen to your body's natural satiety cues to know when you are hungry or full at first. Try cooking, meal-prepping, and eating with others. Incorporate their support with the food plan to help you keep on track.

Try to focus on having non-distracted eating during meals. This means silencing your cellphone, turning off your TV or computer, and savoring your food.

Mindful eating	<p>Eat/drink with intention</p> <ul style="list-style-type: none"> • How did the food make you feel? • Are you enjoying it? <p>Listen to your hunger/thirst</p> <ul style="list-style-type: none"> • Is your stomach growling? • Are you parched?
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Protocol

Study Title: Integrative Medicine for Hypermobility Spectrum Disorder (HSD) and Ehlers-Danlos (EDS) syndromes: A mixed-methods feasibility study (IMforHSDandEDS)

PI: Douglas Hanes, PhD

IRB #: DH10320/PRAF

Approval Date: 01.05.21

Version: 2.0

	<p>Slow down</p> <ul style="list-style-type: none"> • Slow down for a moment and enjoy your food. This will help you listen to your hunger and get pleasure out of eating. Take your time.
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Sleep: Try to sleep 7-8 hours at night. Practice good sleep hygiene by having a wind-down time at night without electronics (at least 2 hours before bedtime). Avoid eating a heavy meal or drinking alcohol before bed.

Movement (light physical activity): Try to take your lunch break outside or go on a walk after work. It might take some time to build up the energy, so start slowly, maybe 15 minutes a day at first.

Assessing the patient's current self-management strategies for mental health

The Clinical Investigator will determine the mental health needs of participants and make mental health provider referrals as needed. If additional support is required and a referral is made, the Clinical Investigator will revisit these needs and check on progress in follow-up visits.

Patients will also be referred to mental health resources found at the Ehlers-Danlos Society website.

E.6 Measures

Primary Outcome measures:

Feasibility

- Retention rate (proportions of participants completing 5 and 9-week visits)
- Recruitment rate (average number of participants enrolled per month)
- Dropout rate (proportions of participants failing to complete 5 or 9-week visits)

Secondary Outcome measures:

Dietary Adherence/Food Tracking Feasibility (MyFitnessPal food tracking):

- Dietary adherence will be measured by self-reported food tracking through Daily Nutrition Goals in the *MyFitnessPal* app and will be documented at 5 and 9 weeks through the Friends feature. Daily macronutrient contributions will be obtained as percentages of total intake. The suggested macronutrient breakdown for the food plan is 40-50% calories from a carbohydrate source, 35-40 % calories from fat, and 15-20% calories from protein. Weekly recorded consumption of the participant will be compared to this standard for an adherence score. For each of the three macronutrient categories, we will give 2 points if the percentage is within the required range and 1 point if the percentage is within 5% of the required range (maximum 6 points total). A score of 4 and above will be considered adherent to the food plan.

Protocol

Study Title: Integrative Medicine for Hypermobility Spectrum Disorder (HSD) and Ehlers-Danlos (EDS) syndromes: A mixed-methods feasibility study (IMforHSDandEDS)

PI: Douglas Hanes, PhD

IRB #: DH10320/PRAF

Approval Date: 01.05.21

Version: 2.0

- The feasibility of food tracking will be measured by adherence to the recommended use of the app. A threshold of 3 days of reporting per week (including breakfast, lunch, dinner, and snacks) for the 9-week duration of the study will be considered adherent and should provide sufficient data to assess the observance of the recommended food tracking.

Food Plan Feasibility (food plan satisfaction survey collection):

- Any negative outcomes, overall cost-prohibitiveness, support needed, and barriers encountered will be assessed with a food plan satisfaction survey at 5 and 9 weeks that will examine the feasibility of the food plan. Qualitative data will be thematically summarized for representative quotes.

Tertiary Outcome measures:

Pain Visual Analog scale (VAS) collection:

- We will collect subjective pain levels from participants over 9 weeks on a 10-point scale. A pain visual analog scale will give a numeric measurement of pain between “worst pain” and “no pain.”

The Patient-Reported Outcomes Measurement Information System (PROMIS-29):

- We will collect general perception of health status as well as quality of life scores over 9 weeks from participants. The PROMIS-29 is a survey that will give a numeric measurement of physical and mental health status on a scale of 0 to 10 that has been validated in adults with multiple chronic conditions.³⁸

Exploratory measures:

Pain Visual Analog scale (VAS), The Patient-Reported Outcomes Measurement Information System (PROMIS-29), and Dietary Adherence associations:

- We will evaluate any associations between symptom severity, perceived pain, health-related quality of life, and dietary composition cross-sectionally and longitudinally over the course of the 9-week intervention.

Patient Assessment of Chronic Illness Care+ scores (PACIC+) collection:

- We will collect general perceptions and attitudes regarding the experiences of chronic illness care and living with chronic illness among patients with HSD and EDS at baseline and 9 weeks.
- The Patient Assessment of Chronic Illness Care (PACIC+) is a validated survey shown to have good reliability, internal consistency, and better psychometric characteristics than other surveys on patient satisfaction.^{39, 40} It is designed to assess the experience and satisfaction within the chronic care model of healthcare, which often results in repeated appointments over a long time interval. It retrospectively assesses experiences of chronic illness care and living with chronic illness over the past 6 months.

Health history and anthropometric measurements:

Protocol

Study Title: Integrative Medicine for Hypermobility Spectrum Disorder (HSD) and Ehlers-Danlos (EDS) syndromes: A mixed-methods feasibility study (IMforHSDandEDS)

PI: Douglas Hanes, PhD

IRB #: DH10320/PRAF

Approval Date: 01.05.21

Version: 2.0

- Biological information will be captured regarding the patients' previous medical health history, age, sex, and gender at the baseline screening. We will also document BMI, weight, height, and estimated energy requirement measurements at baseline. We will record patient self-reported weight at 5 and 9 weeks and track any changes that occur. Any abnormal BMI values will be monitored appropriately for safety, and any changes in these measures will be analyzed in accordance with the overall effectiveness of the diet.
- We will also document any other patient-reported symptoms that are experienced in addition to HSD or EDS throughout the 9 weeks and document any changes that occur.
- Any current pain medications or supplements that the participants are taking for pain will also be recorded.

Beighton score: range of motion measurements

- A set of measurements that assess joint hypermobility through a 9-point scale will be documented during the in-office screening. For every joint that can be extended past a specified angle, 1 point is added to the patient's Beighton score. A score of 4 or more indicates that generalized joint hypermobility is present.¹⁴
- The Beighton score will be obtained during the baseline screening.

NUNM Multi-system Adverse Event questionnaire:

- A multi-system AE questionnaire will be administered at each visit. As HSD and EDS are associated with a considerable list of comorbidities, we will obtain a baseline measure of the AE questionnaire for each participant so that we have documented any pre-existing conditions. We will check on these conditions throughout the 9 weeks to ensure that symptoms have not worsened, in addition to noting any new occurrences. We will monitor these symptoms closely and recommend cessation of the food plan if a patient feels that any of their symptoms have been exacerbated.
- Participants will also be assessed for any adverse events during check-in calls with the following question, "Are you experiencing any new symptoms or side-effects that you may have noticed?" We will recommend cessation of the food plan if a patient feels that any of their symptoms have been exacerbated, or if they are experiencing any new symptoms.
- Dietary alterations involving increased fats, protein, fruits, and vegetables may cause gastrointestinal distress. HSD and EDS are associated with motility issues that may result in constipation; however, adherence to a Mediterranean-style food pattern has been associated with improved gastrointestinal symptoms.⁴¹ We will monitor these symptoms closely and recommend cessation of the food plan if a patient is experiencing significant digestive distress.

E.7 Data Collection and Sources

E.7.1 Confidentiality and Data Storage

There is a very small risk that information about a study participant could be inadvertently disclosed to non-study personnel. Throughout the study, measures to ensure the privacy of information on study subjects will be maintained. All study investigators and staff have been certified in the use of human

Protocol

Study Title: Integrative Medicine for Hypermobility Spectrum Disorder (HSD) and Ehlers-Danlos (EDS) syndromes: A mixed-methods feasibility study (IMforHSDandEDS)

PI: Douglas Hanes, PhD

IRB #: DH10320/PRAF

Approval Date: 01.05.21

Version: 2.0

subjects in research and have received training in HIPAA regulations. Participants and staff will be informed of the confidentiality of information and assured that data will be used only for statistical purposes and group analyses in which the individual cannot be identified. No data beyond what is stated in the informed consent will be sought without authorization from the participant. Information on illnesses and hospitalizations will not be sought from hospitals or doctors without a signed medical release from the subject. Conversely, no information on any individual will be released to anyone other than study personnel without a signed medical release from the participant, or where appropriate, the next of kin or a physician in case of a life-threatening emergency to the subject. All study personnel will be instructed not to discuss any participants with persons other than study personnel.

Each participant will be assigned a unique alpha-numeric ID upon screening. All data resulting from study visits will be collected on standardized case report forms (CRFs). Data will be transferred from CRFs to a secure REDCap database for data management. Outcome data from *MyFitnessPal* will be entered into the REDCap database by the student researcher. Data will be downloaded only onto a password protected computer; upon download, data will be immediately entered into REDCap and deleted from the hard drive. Food VAS, Patient Assessment of Chronic Illness Care (PACIC+), and PROMIS-29 surveys will all be recorded utilizing the REDCap database. REDCap is a secure, web-based application that supports electronic data capture for research studies. REDCap features include: 1) intuitive data entry features; 2) audit trails for tracking data manipulation and export; 3) user-based privileges that support HIPAA compliance; 4) seamless data export to common statistical packages; and 5) procedures for importing data from external sources. The REDCap database will be accessible only by the study team. The link between study IDs and protected health information will be kept as a single electronic file stored on a limited-access electronic folder on a secure server with select access limited to the study team. Data will be destroyed 3 years after completion of the study. Computer files will be deleted from the server, and paper files will be destroyed using a professional document shredding service.

All completed forms will be kept in locked files to which only project personnel have access. These files will also be in locked rooms. Data from paper forms will be manually entered into REDCap and kept as electronic files. Paper forms will continue to be stored in a locked cabinet up to completion of data analysis, at which point they will be shredded. Electronic files will be password protected with access given to study personnel only. All analyses will be conducted by study staff at the Helfgott Research Institute. The study statistician will only access de-identified data exported from REDCap. Only de-identified data will be presented in any reports, presentations, or manuscripts.

E.8 Risks and Benefits

In the USDA 2015-2020 Dietary Guidelines for Americans, the Mediterranean diet was listed among the Healthy Style Eating Pattern for its association with positive health outcomes.³⁰ “The Healthy U.S.-Style Eating Pattern is designed to meet the Recommended Dietary Allowances (RDA) and Adequate Intakes for essential nutrients, as well as Acceptable Macronutrient Distribution Ranges (AMDR) set by the Food and Nutrition Board of the IOM. This eating pattern also conforms to limits set by the IOM or *Dietary*

Protocol

Study Title: Integrative Medicine for Hypermobility Spectrum Disorder (HSD) and Ehlers-Danlos (EDS) syndromes: A mixed-methods feasibility study (IMforHSDandEDS)

PI: Douglas Hanes, PhD

IRB #: DH10320/PRAF

Approval Date: 01.05.21

Version: 2.0

Guidelines, for other nutrients or food components and nutritional goals for almost all nutrients are met.”⁴² The anti-inflammatory food plan that will be recommended in this 9-week integrative medicine intervention reflects macronutrient levels that are similar to those of a Mediterranean diet, which breaks down to 40-50% carbohydrates, 15-20% protein, and 25-30 % fat.²⁹ This macronutrient breakdown would still meet the requirements for carbohydrate restriction in conditions like type 2 diabetes, which is usually around 50 grams per day.⁴³

The Mediterranean-style eating pattern is one of the most studied diets and has amassed a large evidence base for the treatment and prevention of many chronic diseases. In a meta-analysis of 50 studies, the diet was associated with improved outcomes for reducing risk factors for cardiovascular disease, such as preventing metabolic syndrome, reducing blood pressure, lipid levels, and endothelial dysfunction; through both the antioxidant and anti-inflammatory properties of foods found in the Mediterranean dietary pattern.⁴⁴ Adherence to a Mediterranean diet has also been shown to be beneficial for individuals with chronic kidney disease (CKD) and has been shown to improve both survival rates and renal function.⁴⁵ In a holistic study of adherence to the Mediterranean diet, it was found to be associated with a 17-25% increase in overall survival rates as well as increased mortality rates for cancer, coronary artery disease, and cardiovascular disease.⁴⁶

Alteration of fats, protein, fruits, and vegetables may increase the risk of gastrointestinal distress that may result in gas, bloating, or constipation. Participants will be advised to discontinue the food plan if the patient is experiencing significant digestive distress.

While the safety of integrative medicine is dependent on individual therapies or treatments, mind-body practices and light movement exercises are generally considered to be safe.⁴⁷ The Clinical Investigator will evaluate the participant’s current supplements and medications before making food plan recommendations to prevent any drug interactions that could occur.⁴⁷

Participants enrolled in the 9-week integrative medicine intervention will receive 3 complimentary office visits and 2 check-in calls from the student researcher. There may be little direct benefits to the participants other than the personal satisfaction of contributing to health research; however, if they respond positively to integrative care, and it was it effective in reducing pain and improving quality of life among patients, it is possible that some of the symptoms associated with the disorder could show some relief.

E.9 Statistical Analysis

All measures collected in the study, including baseline characteristics and outcome measures, will be summarized using mean and SD (biomarkers, anthropometrics), median and IQR (Beighton score), or percentage within each level, for categorical variables. All statistical analyses will be performed at the National University of Natural Medicine.

For Specific Aim 1,

Protocol

Study Title: Integrative Medicine for Hypermobility Spectrum Disorder (HSD) and Ehlers-Danlos (EDS) syndromes: A mixed-methods feasibility study (IMforHSDandEDS)

PI: Douglas Hanes, PhD

IRB #: DH10320/PRAF

Approval Date: 01.05.21

Version: 2.0

Feasibility of the 9-week integrative medicine intervention will be measured through recruitment and retention at each follow-up visit. Recruitment rate will be presented as the mean number of participants enrolled per month, with enrolment ceasing either after 4 months, or when n=20 participants have been enrolled. Retention will be calculated as the percentage of enrolled participants from whom follow-up data is obtained, at either the 5-week or 9-week visit.

For Specific Aim 2,

Adherence to the recommended diet will be assessed in different ways and tracked by macronutrient levels and dietary composition. In particular, we will assess:

- Percentage of days on which the diet recommendations were met; in order to satisfy this requirement, macronutrient distribution must meet all of the following:
 - Carbohydrates between 40-50%
 - Protein between 15-20%
 - Fat between 25-30 %
- Number of weeks in which recommendations were met at least 5 days;
- Whether recommendations were met on at least 75% of total days (Y/N)
- Mean of weekly adherence scores calculated over the 9-week study period.

Percentage of days and weeks adherent will be summarized across participants as median/IQR/range. We will also present the percentage of participants who met the threshold of 75% days adherent.

Feasibility of the 9-week integrative medicine intervention will also be measured through self-reported food plan satisfaction surveys that assess any negative outcomes, overall cost-prohibitiveness or burden, support needed, and any barriers that are encountered with the recommended dietary modifications.

- Because these measures are reported as open responses, they will be thematically summarized for representative quotes, at each time point measured.

Adherence with dietary tracking will be assessed by:

- Percentage of total days on which dietary intake was documented. Self-reporting of daily dietary intake on at least 50% of total days will be considered adherent.
- Number of weeks on which intake was self-reported at least 3 days.

For Specific Aim 3,

We will test whether the integrative medicine education intervention reduced pain and improved health-related quality of life in patients with HSD or EDS. VAS pain scores and PROMIS-29 domain scores will be summarized across participants and time points as mean (SD).

Protocol

Study Title: Integrative Medicine for Hypermobility Spectrum Disorder (HSD) and Ehlers-Danlos (EDS) syndromes: A mixed-methods feasibility study (IMforHSDandEDS)

PI: Douglas Hanes, PhD

IRB #: DH10320/PRAF

Approval Date: 01.05.21

Version: 2.0

Analysis of pain and HRQoL outcomes for Aim 2 will use paired t-tests to assess mean changes unless investigation of distributions indicates a need for nonparametric testing, in which case changes will be analyzed using Wilcoxon signed-rank tests.

For Exploratory Aim 1,

Any associations between pain, HRQoL, and diet will be assessed both cross-sectionally and longitudinally over the course of treatment. Cross-sectional associations of VAS pain score, PROMIS-29 domain scores, and dietary composition measures will be analyzed using Pearson correlations (or Spearman correlations for badly non-normal data). To assess associations of longitudinal changes, we will compute changes in each measure both from baseline to 5 weeks, and from baseline to 9 weeks, and we will similarly evaluate correlations between the changes over each time period.

Cross-sectional correlations assess the association of participants' ordinary diet with pain and health-related quality of life, while correlations of changes assess the association of dietary changes, in response to the treatment recommendations, with changes in pain and HRQoL over the same time frame.

We will also assess associations between age, race, sex, baseline symptoms, and changes in outcomes at follow-up, using Pearson correlations and independent t-tests, as appropriate.

For Exploratory Aim 2,

We will summarize Patient Assessment of Chronic Illness Care (PACIC+) scores in the sample, at both baseline and study end, and mean (SD). We will also test whether the scoring changed after participating in integrative medicine intervention, using a paired t-test.

F. Conclusion, Summary and/or Benefits of the Knowledge Gained

Hypermobility Spectrum Disorder (HSD) and Ehlers-Danlos syndromes (EDS) are debilitating conditions of the connective tissue that can be both physically and psychologically disabling. For chronic care conditions, there is a need beyond the current healthcare model for patient-centered pain prevention and management programs. There are no current published scientific studies on holistic care among patients living with HSD or EDS, nor is there any research on dietary intake and its impact on the disorder. In order to better support rehabilitation, healthcare professionals should not only become more aware of both HSD and EDS and their related comorbidities, but they should also be educated in an effort to support the psychosocial needs that accompany chronic pain conditions. This project would allow us to study a novel integrative medicine intervention that is comprehensive, holistic, and patient-centered.

This study will allow us to capture the recruitment potential and retention rate among patients with Hypermobility Spectrum Disorder (HSD) or Ehlers-Danlos syndromes (EDS) participating in a 9-week

Protocol

Study Title: Integrative Medicine for Hypermobility Spectrum Disorder (HSD) and Ehlers-Danlos (EDS) syndromes: A mixed-methods feasibility study (IMforHSDandEDS)

PI: Douglas Hanes, PhD

IRB #: DH10320/PRAF

Approval Date: 01.05.21

Version: 2.0

integrative medicine intervention that is comprised of a prescribed anti-inflammatory (Mediterranean) food plan as well as general behavioral and psychosocial support. Both quantitative and qualitative measures obtained by participant food tracking and food satisfaction surveys will allow us to assess adherence to and feasibility of the prescribed food plan, as well as the feasibility of mobile device food tracking. This study aims to recruit 20 patients with HSD or EDS and make preliminary observations regarding the effects of integrative medical care on pain reduction and improved quality of life. We will capture current patient assessments of chronic illness care and living with a chronic illness among patients with HSD or EDS as well any associations between pain, quality of life, and diet. If the 9-week integrative medicine intervention shows the potential to be an appropriate program for patients with HSD or EDS, results from this study could be used to inform the healthcare community around ways to better support this unique population, and those same methods could be translated into a larger study and may contribute to further scientific research.

References

1. Castori M. Ehlers-Danlos Syndrome, Hypermobility Type: An Underdiagnosed Hereditary Connective Tissue Disorder with Mucocutaneous, Articular, and Systemic Manifestations. *ISRN Dermatol.* 2012;2012:1-22. doi:10.5402/2012/751768
2. Corrado B, Ciardi G. Hypermobility Ehlers-Danlos syndrome and rehabilitation: taking stock of evidence based medicine: a systematic review of the literature. *J Phys Ther Sci.* 2018;30(6):843-847. doi:10.1589/jpts.30.847
3. Chopra P, Tinkle B, Hamonet C, et al. Pain management in the Ehlers–Danlos syndromes. *Am J Med Genet Part C Semin Med Genet.* 2017;175(1):212-219. doi:10.1002/ajmg.c.31554
4. Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers–Danlos syndromes. *Am J Med Genet Part C Semin Med Genet.* 2017;175(1):8-26. doi:10.1002/ajmg.c.31552
5. Ehlers-Danlos syndrome - Genetics Home Reference - NIH. <https://ghr.nlm.nih.gov/condition/ehlers-danlos-syndrome#statistics>. Accessed July 11, 2020.
6. Demmler JC, Atkinson MD, Reinhold EJ, Choy E, Lyons RA, Brophy ST. Diagnosed prevalence of Ehlers-Danlos syndrome and hypermobility spectrum disorder in Wales, UK: a national electronic cohort study and case-control comparison. *BMJ Open.* 2019;9(11):31365. doi:10.1136/bmjopen-2019-031365
7. Weerakkody RA, Vandrovcova J, Kanonidou C, et al. Targeted next-generation sequencing makes new molecular diagnoses and expands genotype-phenotype relationship in Ehlers-Danlos syndrome. *Genet Med.* 2016;18(11):1119-1127. doi:10.1038/gim.2016.14
8. Hershenfeld SA, Wasim S, McNiven V, et al. Psychiatric disorders in Ehlers–Danlos syndrome are frequent, diverse and strongly associated with pain. *Rheumatol Int.* 2016;36(3):341-348. doi:10.1007/s00296-015-3375-1
9. Hakim AM, Grahame R. 6 Joint hypermobility Emeritus professor of Clinical Rheumatology and Consultant Rheumatologist. 2004;17(6):989-1004. doi:10.1016/S1521-6942(03)00108-6
10. Seneviratne SL, Maitland A, Afrin L. Mast cell disorders in Ehlers–Danlos syndrome. *Am J Med Genet Part C Semin Med Genet.* 2017;175(1):226-236. doi:10.1002/ajmg.c.31555

Protocol

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PI: Douglas Hanes, PhD

IRB #: DH10320/PRAF

Approval Date: 01.05.21

Version: 2.0

11. Bennett SE, Walsh N, Moss T, Palmer S. Understanding the psychosocial impact of joint hypermobility syndrome and Ehlers–Danlos syndrome hypermobility type: a qualitative interview study. *Disabil Rehabil.* 2019;0(0):1-10. doi:10.1080/09638288.2019.1641848
12. Bulbena A, Gago J, Pailhez G, Sperry L, Fullana MA, Vilarroya O. Joint hypermobility syndrome is a risk factor trait for anxiety disorders: A 15-year follow-up cohort study. *Gen Hosp Psychiatry.* 2011;33(4):363-370. doi:10.1016/j.genhosppsych.2011.03.004
13. Lumley MA, Jordan M, Rubenstein R, Tsipouras P, Evans MI. Psychosocial functioning in the Ehlers-Danlos syndrome. *Am J Med Genet.* 1994;53(2):149-152. doi:10.1002/ajmg.1320530206
14. Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). *Am J Med Genet.* 1998;77(1):31-37. <http://www.ncbi.nlm.nih.gov/pubmed/9557891>.
15. Juul-Kristensen B, Schmedling K, Rombaut L, Lund H, Engelbert RHH. Measurement properties of clinical assessment methods for classifying generalized joint hypermobility-A systematic review. *Am J Med Genet Part C Semin Med Genet.* 2017;175(1):116-147. doi:10.1002/ajmg.c.31540
16. Levy HP. Ehlers-Danlos Syndrome, hypermobility type Summary Genetic counseling Suggestive findings. *GeneReviews.* 2018:1-28. https://www.dropbox.com/s/dcx1u1j3mxc0b8i/Bookshelf_NBK1279.pdf?dl=0.
17. Voermans NC, Knoop H, Bleijenberg G, Van Engelen BG. Pain in Ehlers-Danlos Syndrome is common, severe, and associated with functional impairment. *J Pain Symptom Manage.* 2010;40(3):370-378. doi:10.1016/j.jpainsymman.2009.12.026
18. Rombaut L, Scheper M, De Wandele I, et al. Chronic pain in patients with the hypermobility type of Ehlers–Danlos syndrome: evidence for generalized hyperalgesia. *Clin Rheumatol.* 2015;34(6):1121-1129. doi:10.1007/s10067-014-2499-0
19. Kostova Z, Caiata-Zufferey M, Schulz PJ. The impact of social support on the acceptance process among RA patients: a qualitative study. *Psychol Health.* 2014;29(11):1283-1302. doi:10.1080/08870446.2014.925895
20. Bovet C, Carlson M, Taylor M. Quality of life, unmet needs, and iatrogenic injuries in rehabilitation of patients with Ehlers-Danlos Syndrome hypermobility type/Joint Hypermobility Syndrome; Quality of life, unmet needs, and iatrogenic injuries in rehabilitation of patients with Ehlers-Danlos Syndrome hypermobility type/Joint Hypermobility Syndrome. doi:10.1002/ajmg.a.37774
21. Rodgers KR, Gui J, Dinulos MBP, Chou RC. Ehlers-Danlos syndrome hypermobility type is associated with rheumatic diseases. *Sci Rep.* 2017;7(November 2016):1-7. doi:10.1038/srep39636
22. Zoppi N, Chiarelli N, Binetti S, Ritelli M, Colombi M. Dermal fibroblast-to-myofibroblast transition sustained by $\alpha\text{v}\beta 3$ integrin-ILK-Snail1/Slug signaling is a common feature for hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorders. *Biochim Biophys Acta - Mol Basis Dis.* 2018;1864(4):1010-1023. doi:10.1016/j.bbadis.2018.01.005
23. Barbaresko J, Koch M, Schulze MB, Nöthlings U. Dietary pattern analysis and biomarkers of low-grade inflammation: a systematic literature review. *Nutr Rev.* 2013;71(8):511-527. doi:10.1111/nure.12035

Protocol

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Version: 2.0

24. Baeza-Velasco C, Bulbena A, Polanco-Carrasco R, Jaussaud R. Cognitive, emotional, and behavioral considerations for chronic pain management in the Ehlers–Danlos syndrome hypermobility-type: a narrative review. *Disabil Rehabil.* 2019;41(9):1110-1118. doi:10.1080/09638288.2017.1419294
25. Vision, Mission & History | AIHM. <https://aihm.org/page/vision/>. Accessed July 19, 2020.
26. Doctor Visits and Getting Medicines | COVID-19 | CDC. <https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/doctor-visits-medicine.html>. Accessed August 21, 2020.
27. Assessing Your Weight | Healthy Weight, Nutrition, and Physical Activity | CDC. <https://www.cdc.gov/healthyweight/assessing/index.html>. Accessed October 8, 2020.
28. Nelms M, Sucher KP, Lacey K, Roth SL. *Nutrition Therapy and Pathophysiology 2e.*; 2012. doi:http://dx.doi.org/10.1016/j.dza.2012.08.018
29. Davis C, Bryan J, Hodgson J, Murphy K. Definition of the mediterranean diet: A literature review. *Nutrients.* 2015;7(11):9139-9153. doi:10.3390/nu7115459
30. Appendix 4. USDA Food Patterns: Healthy Mediterranean-Style Eating Pattern - 2015-2020 Dietary Guidelines | health.gov. <https://health.gov/our-work/food-nutrition/2015-2020-dietary-guidelines/guidelines/appendix-4/>. Accessed July 20, 2020.
31. Young S. Healthy behavior change in practical settings. *Perm J.* 2014;18(4):89-92. doi:10.7812/TPP/14-018
32. MyFitnessPal | MyFitnessPal.com. <https://www.myfitnesspal.com/>. Accessed August 20, 2020.
33. Ferrara G, Kim J, Lin S, Hua J, Seto ; Edmund, Seto E. A Focused Review of Smartphone Diet-Tracking Apps: Usability, Functionality, Coherence With Behavior Change Theory, and Comparative Validity of Nutrient Intake and Energy Estimates. doi:10.2196/mhealth.9232
34. Bracken ML, Waite BM. Self-Efficacy and Nutrition-Related Goal Achievement of MyFitnessPal Users. *Heal Educ Behav.* June 2020:109019812093626. doi:10.1177/1090198120936261
35. Fakih El Khoury C, Karavetian M, Halfens RJG, Crutzen R, Khoja L, Schols JMGA. The Effects of Dietary Mobile Apps on Nutritional Outcomes in Adults with Chronic Diseases: A Systematic Review and Meta-Analysis. *J Acad Nutr Diet.* 2019;119(4):626-651. doi:10.1016/j.jand.2018.11.010
36. Heo S, McSweeney J, Prewitt TE, et al. A Tailored Dietary Sodium Intervention Using Technology and Psychosocial Support: A Pilot Study. *J Cardiovasc Nurs.* 2019;34(2):137-140. doi:10.1097/JCN.0000000000000537
37. Payne HE, Lister C, West JH, Bernhardt JM. Behavioral Functionality of Mobile Apps in Health Interventions: A Systematic Review of the Literature. doi:10.2196/mhealth.3335
38. Rose AJ, Bayliss E, Huang W, et al. Evaluating the PROMIS-29 v2.0 for use among older adults with multiple chronic conditions. *Qual Life Res.* 2018;27(11):2935-2944. doi:10.1007/s11136-018-1958-5
39. Glasgow RE, Wagner EH, Schaefer J, Mahoney LD, Reid RJ, Greene SM. Development and Validation of the Patient Assessment of Chronic Illness Care (PACIC). *Med Care.* 2005;43(5):436-444. doi:10.1097/01.mlr.0000160375.47920.8c
40. Vrijhoef HJM, Berbee R, Wagner EH, et al. Quality of integrated chronic care measured by patient survey: identification, selection and application of most appropriate instruments. doi:10.1111/j.1369-7625.2009.00557.x

Protocol

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Version: 2.0

41. Zito FP, Polese B, Vozzella L, et al. Good adherence to mediterranean diet can prevent gastrointestinal symptoms: A survey from Southern Italy. *World J Gastrointest Pharmacol Ther.* 2016;7(4):564. doi:10.4292/wjgpt.v7.i4.564
42. A Closer Look Inside Healthy Eating Patterns - 2015-2020 Dietary Guidelines | health.gov. https://health.gov/our-work/food-nutrition/2015-2020-dietary-guidelines/guidelines/chapter-1/a-closer-look-inside-healthy-eating-patterns/?mbid=synd_msnhealth. Accessed August 25, 2020.
43. Accurso A, Bernstein RK, Dahlqvist A, et al. Dietary carbohydrate restriction in type 2 diabetes mellitus and metabolic syndrome: Time for a critical appraisal. *Nutr Metab.* 2008;5(1):9. doi:10.1186/1743-7075-5-9
44. Kastorini CM, Milionis HJ, Esposito K, Giugliano D, Goudevenos JA, Panagiotakos DB. The effect of mediterranean diet on metabolic syndrome and its components: A meta-analysis of 50 studies and 534,906 individuals. *J Am Coll Cardiol.* 2011;57(11):1299-1313. doi:10.1016/j.jacc.2010.09.073
45. Chauveau P, Aparicio M, Bellizzi V, et al. Mediterranean diet as the diet of choice for patients with chronic kidney disease. *Nephrol Dial Transplant.* 2018;33(5):725-735. doi:10.1093/ndt/gfx085
46. Ravera A, Carubelli V, Sciatti E, et al. Nutrition and cardiovascular disease: Finding the perfect recipe for cardiovascular health. *Nutrients.* 2016;8(6). doi:10.3390/nu8060363
47. Safe Use of Complementary Health Products and Practices | NCCIH. <https://www.nccih.nih.gov/health/safety>. Accessed August 21, 2020.

Protocol

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